REMARKS/ARGUMENTS

Claims 1 and 3-66 are pending in the captioned application. Claims 1 and 3-12 are under examination. Applicants hereby cancel the non-elected claims 13-66. Applicants reserve the right to prosecute these claims in one or more divisional applications.

Claim 4 stands rejected under 35 U.S.C. §112, second paragraph, as being indefinite for containing trademarks. In response, Applicants have amended the claims to remove the references of the trademarks. Specifically, Sequenase has been replaced with the generic name T7 DNA polymerase exo$^-$ (See, e.g. http://www.usbweb.com/, under Sequenase™ Version 2.0 DNA Polymerase). Thermo Sequenase I has been replaced with the generic name Taq DNA polymerase F667Y deletion 1-235 (US 5,614,365 and US 5,885,813). Thermo Sequenase II has been replaced with the generic name Thermus thermophilus F667Y D18A DNA polymerase (US 6,479,267). ThermoSequenase E681M has been replaced with the generic name Taq F667Y D18A E681M DNA polymerase (EP 1210440). Applicants respectfully submit that in view of these amendments, this rejection should now be withdrawn.

Claims 5-7 stand rejected under 35 U.S.C. §112, as allegedly containing new matter. In addition, claims 1 and 5-12 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully disagree. However, in an effort to expedite prosecution,

Applicants have amended the claims to remove the rejected language. Applicants submit that these rejections are now moot.

Claims 1 and 3-12 stand rejected under 35 U.S.C. §112, first paragraph, for allegedly lack of enablement. Applicants respectfully disagree.

In response, Applicants submit that in an effort to expedite examination, and without admitting to the adequacy of the Examiner's *prima facie* case of unpatentability, Applicants have amended the claims. Claim 1 has been amended to remove reference to ligase, telomerase or primase, and now only claims the use of a template dependent DNA polymerase for the method. As the Examiner pointed out, the claims are enabling for methods using a variety of DNA polymerases. As such, Applicants submit that the amended claims are enabling and the 112, first paragraph rejection should now be withdrawn.

Applicants submit that, as the Examiner pointed out, the specification has reasonably provided evidence that manganese can significantly increase the ability of Thermo Sequenase I (TS I), Thermo Sequenase II (TS II), Phi 29 exo$^-$, AmpliTaq, Thy b, and TS EM polymerase to incorporate terminal phosphate labeled nucleotides. This list of enzymes include both Family A and Family B DNA polymerases (Phi 29 exo$^-$ is a Family B DNA polymerase while the rest are Family A polymerase). Furthermore, it also includes both thermostable and non-thermostable DNA polymerases (e.g., while the majority are thermostable enzymes, Phi 29 is not). As such, Applicants submit that the specification is enabling for template dependent DNA polymerases in general.

Applicants also submit that the specification provides additional evidence that manganese increases the ability for terminal phosphate labeled nucleotide incorporation by even a broader list of DNA polymerases. Specifically, Table 5 (Example 15) provides a list of DNA polymerases used, in the presence of manganese, for the evaluation of incorporation of modified dNTPs. This list includes several of the enzymes the Examiner mentioned in the office action (See above). It also includes multiple other enzymes (e.g., Klenow, AMV RT, Human DNA polymerase beta, etc). It clearly shows that these other enzymes behave similarly as well. An analysis of these enzymes shows that they represent a full range of DNA polymerases, from Families A, B, X and RT. The enzymes cover a variety of organisms of origin, spanning retrovirus, bacteriophage, bacteria, archaea and human. A summary of these additional enzymes is presented in a table below. Applicants submit that the specification, considered as a whole, is enabling for the claimed method.

Short Name	**Long Name**	**Tradename**	**Category**	**Family**
T7 exo-	T7 DNA polymerase deletion 118-145	Sequenase v2.0 (USB)	Bacteriophage	A
Klenow (exo-)	Large fragment of E. coli DNA polymerase I, 3'-5' exonuclease deficient mutant	-	Bacteria	A
AMV RT	Reverse Transcriptase from Avian Myeloblastosis Virus	-	Retrovirus	RT
9°N	DNA polymerase mutant with reduced 3'-5' exonuclease isolated from *Thermococcus* sp. (strain 9°N-7)	°N_m™ DNA Polymerase (New England Biolabs)	Thermostable polymerase from archaea	B
Tsp JS1	DNA polymerase I from uncharacterized Thermus species	-	Thermostable polymerase from bacteria	A
Delta	Thermoanaerobacter tengcongensis	-	Thermostable	A

T10, Tten	DNA polymerase I		polymerase from bacteria	
Pfu	Pyrococcus furiosis DNA polymerase	-	Thermostable polymerase from archaea	B
Tsu	Thermotoga subterranean DNA polymerase I	-	Bacteria	A
Tne	Theremotoga neapolitana DNA polymerase I	-	Bacteria	A
Ttm	Theremotoga thermarium DNA polymerase I	-	Bacteria	A
Pol β	Human DNA polymerase beta	-	Human	X

Claims 1, 3 and 5-7 stand rejected under 35 U.S.C. §102(b) as being anticipated by Yarbrough et al. (JBC 1979, 254(23):12069-73). Applicants respectfully disagree. However, in an effort to expedite prosecution, and without admission express or implied that the rejection is properly founded, Applicants have amended the claims. Applicants submit that in view of the amendments, this rejection is now moot.

Claims 1, 3 and 5-10 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Wu et al. (Arch. Biochem Biophys. 1986, 246(2):564-71), Bernard et al. (Biochem BIophys Acta. 1977 478(4):407-16), in further view of Yarbrough et al. Applicants respectfully disagree. However, in an effort to expedite prosecution, and without admission express or implied that the rejection is properly founded, Applicants have amended the claims. Applicants submit that in view of the amendments, this rejection is now moot.

Claims 1, 3-7, 11 and 12 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Hardin (US2003/0064366A1) in view of McGuigan (Methods Enzymol. 1993; 218:241-58). Applicants respectfully disagree,

Applicants submit that Examiner's analysis of McGuigan seems flawed. The Examiner states that McGuigan teaches that upon addition of manganese[1] to a Sequenase reaction system, "the polymerase incorporates ddNTPs at a greater rate". Examiner finds support of this conclusion on page 247 of the reference, in the section entitled "Enzymes". However, a closer look at this section, as well as the entire reference suggests otherwise.

In the section the Examiner referred to, McGuigan states that "Tabor and Richardson[11] discovered that substituting Mn^{2+} for Mg^{2+} reduces the discrimination against dideoxynucleotides for T7 DNA polymerase". This prompted McGuigan to try Sequenase, which is a mutated form of T7 DNA polymerase. When they substituted Mg^{2+} with Mn^{2+}, they found that "Sequenase produced fingerprints that are slightly stronger and more even than the fingerprints obtained with reverse transcriptase." From this discussion, Applicants submit that it is unclear how the Examiner reached the conclusion, e.g. "the polymerase incorporates ddNTPs at a greater rate"

[1] The Office Action on pages 18-19 used "magnesium" in several occasions, where the metal ion "manganese" was clearly the topic being discussed. Applicants focus the discussion here on manganese as it is a key part of the claimed invention as illustrated in Claim 1.

[11] S. Tabor and C.C. Richardson, cited by Examiner in the same Office Action, page 11 (Proc Natl Acad Sci U S A. 86(11):4076-80, 1989).

The effect of manganese in reducing the discrimination of Sequenase (T7 DNA polymerase) for dideoxynucleotides, as compared to deoxynucleotides (as suggested by Tabor or McGuigan), should not be confused with "the polymerase incorporates ddNTPs at a greater rate". Applicants submit that "reducing the discrimination" could be achieved by either a rate increase in incorporating ddNTPs, or a rate decrease in incorporating dNTPs. Tabor and Richardson demonstrate that, T7 DNA polymerase incorporates deoxynucleotides at a much slower rate in the presence of manganese, as compared to in the presence of magnesium (Figure 1). They further demonstrate that when both dideoxynucleotides and deoxynucleotides are present, manganese increases the relative incorporation of dideoxynucleotides by T7 DNA polymerase, as measured by incorporation ratio of deoxynucleotide to dideoxynucleotide (Table 1). Applicants submit that from this report, it is premature to conclude that at the presence of manganese, "the polymerase incorporates ddNTPs at a greater rate".

Applicants submit that a skilled person in the art, considering McGuigan in light of Tabor and Richardson, could not have reached the conclusion that at the presence of manganese, "the polymerase incorporates ddNTPs at a greater rate". In addition, Applicants submit that McGuigan uses base-labeled ddNTPs in their study (See page 246, section entitled "Labeled Dideoxynucleotides"). Applicants submit that the effect of manganese on the incorporation of base-labeled ddNPTs is similar to the effect shown by Tabor and Richardson, e.g. manganese slows down incorporation as compared to

magnesium (see figure 3 of current specification). In this regard, Applicants submit that McGuigan actually teaches away from the combination of Hardin and McGuigan.

Early and favorable consideration is respectfully requested.

Respectfully submitted,

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